



Ocular involvement in atopic disease: a review

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Purpose of review

To provide a review of the potential sight-threatening sequelae associated with ocular involvement of atopic disease and to discuss the management of this chronic condition.

Recent findings

There has been a recognition that atopic keratoconjunctivitis (AKC) is a chronic, inflammatory and potentially blinding disease. Recent efforts have focused on steroid sparing, systemic T cell and calcineurin inhibitor medications for the treatment of severe disease.

Summary

Ocular involvement in atopic disease can have a variety of clinical manifestations. Progressive disease can be vision threatening, especially in younger patients. Prompt and effective treatment through a multidisciplinary approach, including ophthalmology, allergy and immunology and dermatology, can permit stability of the disease.

Keywords

atopic disease, atopic keratoconjunctivitis, clinical manifestations, pathophysiology, treatment

INTRODUCTION

Atopy is the propensity to produce IgE antibodies in response to environmental proteins [1]. The presence of atopy in an individual is associated with an increased risk of systemic manifestations, such as atopic dermatitis, asthma and allergic rhinitis, as well as ocular manifestations, namely keratoconjunctivitis [2]. Atopic keratoconjunctivitis (AKC), first described by Hogan [3] in 1953, can be distinguished from seasonal or perennial allergic conjunctivitis and vernal conjunctivitis as a chronic, inflammatory, cicatrizing conjunctivitis with potentially severe ocular sequelae.

PATHOGENESIS

Chronic atopic conjunctival disease is a type IV hypersensitivity immune reaction, with a predominantly T-cell-mediated response. T cells are triggered by antigen presentation, or by cytokines including IL-4, IL-5 and IL-13, to differentiate into Th2 cells, the effector of the acute response. Th2 cells increase the circulating IgE eosinophil levels, as well as produce cytokines, including IL-12, that induce Th1 cell production, the effector of the chronic phase [4]. This theory is supported by in situ hybridization and flow cytometry studies using conjunctival epithelium and tears of human participants with AKC [5–7].

AKC is a chronic inflammatory condition that is primarily a Th1 response [8]. Th1 cells produce IFN γ ,

IL2 and IL-12, all of which further induce Th1 production, prompt chemotaxis, and further eosinophil production. Eosinophils are a key mediator in the process with the generation of cytokines and chemokines that affect their own production as well as other leukocytes [9]. Many cells, cytokines and adhesion molecules have been implicated in the process including IL-8, RANTES adhesion molecule, IL-33, basophils and thymic stromal lymphopoietin [10–12].

As with atopic dermatitis, AKC can be exacerbated by dryness leading to an itch-scratch cycle that increases inflammation [13].

Recent studies have also suggested that the clinical presentation of AKC may be influenced by microbes. *Staphylococcal aureus* may play a role in the activation of inflammatory cells via the toll like receptor. This is supported by human data showing a higher frequency of colonization with *S. aureus* in

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KEY POINTS

- AKC is a chronic and potentially blinding condition.
- The pathophysiology of AKC is a T-cell mediated process.
- Treatment with systemic tacrolimus can be indicated for severe cases.

individuals with AKC compared with controls. In addition, in a mouse model of AKC, conjunctivitis develops more rapidly and higher levels of tear cytokines are seen if *S. aureus* is present versus absent on the ocular surface [14].

CLINICAL PRESENTATION

AKC typically presents with a constellation of symptoms including ocular pain, erythema, ropy or mucoid discharge, itching, tearing, burning, photophobia and visual disturbances [15,16]. Patients can be as young as in their first decade of life but are traditionally in the late teens to mid-20s. Oftentimes, symptoms can persist into the fourth and fifth decades of life and can recur with seasonal exacerbations, especially in the spring and summer months [17]. AKC is associated with a family history of atopy, along with a personal history of atopic dermatitis and asthma. Although over 95% of AKC patients have eczema and 87% have asthma, the frequency of ocular involvement in patients with atopic dermatitis ranges only from 25 to 42% [16,18].

On examination, signs of AKC can be classified according to the involved anatomic location, namely the eyelids, conjunctiva and cornea.

Eyelids

AKC is associated with atopic dermatitis in nearly 95% of cases [18]. As such, patients often have severe

dermatitis, eczema and hyperpigmentation of the eyelid and periorbital skin. Periorbital skin hyperpigmentation is often referred to as 'panda eyes' and lid thickening and edema can cause formation of linear lid creases known as Dennie–Morgan lines (Fig. 1a). Patients can also have absence of lateral eyebrows known as Hertoghe sign. Eyelid skin scarring can lead to ectropion and entropion formation along with madarosis. Chronic eye irritation can also lead to eyelid edema and reactive ptosis. Associated anterior and posterior blepharitis is also common, causing a thickened and inflamed eyelid margin leading to meibomian gland obstruction and eyelid margin irregularities [16,19].

Conjunctiva

Chronic inflammation of the tarsal and forniceal conjunctiva leads to conjunctival thickening, hyperemia, chemosis and papillary hypertrophy. Papillae are often observed on the upper and lower tarsal conjunctiva (Fig. 1b). In later stages, the papillae can be replaced by diffuse conjunctival scarring, manifesting as foreshortening of the inferior fornices (more often than the medial and lateral fornices) and symblepharon. Limbal Horner-Trantas dots, although more common in vernal keratoconjunctivitis, can be observed as well, especially during seasonal exacerbations [16].

Cornea

Corneal involvement from AKC is often secondary to mechanical trauma from inflamed/scarred conjunctival tissue and/or secondary meibomian gland disease. Corneal manifestations can range from mild superficial punctate keratopathy to decreased corneal sensitivity to progressive corneal erosions, ulcerations, scarring and neovascularization, the latter of which can cause vision loss. Formation of mucous plaques and filaments are common and are attributed to increased mucin (as demonstrated by high

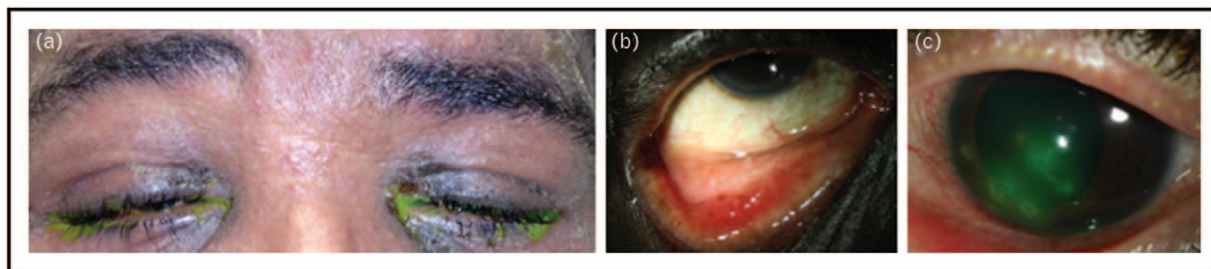


FIGURE 1. (a) Slit lamp photographs of a patient's right eye with atopic keratoconjunctivitis with lid thickening, hyperpigmentation and formation of horizontal lid creases. (b) Slit lamp photograph of patient's right eye with conjunctival papillary hypertrophy in a case of atopic keratoconjunctivitis. (c) Slit lamp photograph of an atopic patient with herpetic keratitis.

Table 1. Table comparing differences in presentation and clinical course between atopic keratoconjunctivitis, vernal keratoconjunctivitis, seasonal/perennial keratoconjunctivitis, and giant papillary conjunctivitis

Condition	Atopic keratoconjunctivitis	Vernal keratoconjunctivitis	Seasonal/perennial keratoconjunctivitis	Giant papillary conjunctivitis
Risk factors	Atopic disease including asthma, atopic dermatitis; family history of atopy	Environmental allergens; typically worse in spring time and in hot and dry environments; males > females	Environmental allergens associated with changes in season or that occur throughout the year: grass, pollen, dust mites, mold, animal dander	Soft contact lens use with poor lens fitting, hygiene or prolonged use; intolerance to contact lens solution; exposed sutures or ocular prosthetic use
Pathophysiology	Inflammatory response secondary to eosinophil, fibroblast, mast cell and lymphocytic activation	Inflammatory response secondary to eosinophil, fibroblast, mast cell and lymphocytic activation	IgE cross-linkage from inciting allergens cause mast cell degranulation and release of inflammatory mediators	Repetitive mechanical irritation
Characteristic clinical presentations	Eyelid thickening and scarring; madarosis; eyelid margin irregularities; conjunctival cicatrization; keratopathy and corneal neovascularization	Cobblestoning of tarsal conjunctiva from papillary hypertrophy; limbal Horner-Trantas dots; shield corneal ulcers; conjunctival scarring, corneal neovascularization	Conjunctival injection, hyperemia, chemosis, mucoid discharge	Papillary hypertrophy of superior tarsal conjunctiva of eye with mechanical irritant; eyelid edema and reactive ptosis
Natural course	Begins in childhood but can persist into fifth decade of life; is chronic in nature with periodic exacerbations	Begins in childhood and resolves during puberty; exacerbations typically occur during spring and summer months	Recurr seasonally with changes in allergens	Directly correlated in inciting risk factors; discontinuation of contact lens use, contact lens solution, removal of prosthesis or sutures can all reduce symptom burden

messenger RNA expression of membrane mucins 1, 2 and 3) [19]. Decreased goblet cell density along with meibomian gland dysfunction can lead to tear film instability and dry eye disease [16,19,20]. Progressive corneal scarring and neovascularization may require penetrating keratoplasty for visual rehabilitation [21]. However, this needs to be approached carefully as limbal stem-cell deficiency can also be present due to repetitive trauma from scarred eyelids.

DIFFERENTIAL DIAGNOSIS

Allergic conjunctival disease is caused by an inflammatory response of the conjunctiva to an allergen and can present as distinctive clinical entities including AKC, vernal keratoconjunctivitis as well as seasonal and perennial keratoconjunctivitis. The differential diagnosis can also include giant papillary conjunctivitis [22[•]]. Of the different clinical entities, AKC is most severe in its clinical presentation and natural course.

Differentiating between these entities relies heavily on patient demographics, inciting risk factors and underlying pathophysiology, signs and symptoms and natural course of the conditions.

Table 1 compares these clinical entities and their distinguishing features [23–26].

Other entities to consider in the differential diagnosis include severe blepharitis, ocular rosacea, alternative causes of conjunctival cicatrization including ocular cicatricial pemphoid, Steven Johnson Syndrome, graft-versus-host disease or prior ocular chemical injury, infectious conjunctivitis, toxic conjunctivitis, phlyctenular conjunctivitis, limbal stem-cell deficiency, dry eye syndrome, keratitis, episcleritis or scleritis.

OCULAR COMPLICATIONS ASSOCIATED WITH ATOPIC KERATOCONJUNCTIVITIS

Chronic AKC can lead to several complications if not treated promptly and effectively. These complications can include cataract formation, blepharitis, glaucoma, keratoconus and infectious keratitis [19].

Cataracts are a common sequela of AKC [27]. The incidence of cataracts in patients with atopic dermatitis ranges from 5 to 38%, with age of onset usually ranging from adolescence to adulthood [28]. Patients often develop anterior subcapsular cataracts, referred to as ‘atopic cataracts’ which are observed 10 years

after disease onset. Posterior subcapsular cataracts occur secondary to long-term oral and topical corticosteroid use. Formation of anterior subcapsular cataracts has been attributed to elevated serum IgE levels as well as -56T allele in the gamma interferon receptor 1 gene promoter which is a potential genetic risk factor [18,29]. Chronic use of corticosteroids is a well established risk factor for the development of cataracts [30]. In fact, patients with asthma who are on high-dose inhaled corticosteroids also appear to have an increased risk for the formation of posterior subcapsular cataracts [31], although this may also be due to improper inhaler usage which results in direct exposure of the eye [32].

Keratoconus often occurs in patients with AKC and the condition has been associated with positive allergy tests [33]. It is exacerbated by chronic eye rubbing due to persistent eye irritation, which is highly associated with atopy. A retrospective study of keratoconus patients found that those who were atopic tended to develop keratoconus at a younger age, suggesting that atopy may be a triggering factor for keratoconus [34]. In patients requiring keratoplasty for progressive corneal thinning and scarring, it has been found that atopic patients have a higher incidence of corneal graft rejection [18]. In addition, postkeratoplasty sclerokeratitis is a severe complication seen in atopic patients undergoing keratoplasty [35]. Patients with atopic dermatitis may also be at higher risk for complications, such as corneal melt, associated with intrastromal corneal ring segments used to treat keratoconus [36].

Patients with AKC have an increased susceptibility to cutaneous and ocular colonization and infection with *S. aureus* (nearly 66–87%) as well as herpes simplex virus. Anterior staphylococcal blepharitis is a common finding in patients with AKC along with staphylococcal bacterial superinfections. Ocular herpes simplex disease occurs with incidence rates as high as 42.5%, is often bilateral, with more severe and frequent recurrences (Fig. 1c) [14,37–39].

Additional ocular complications of AKC include development of glaucoma from long-term steroid use, retinal detachment, though to be secondary to chronic eye rubbing and subsequent trauma [40,41] and uveitis [18]. Atopic diseases are also associated with higher frequency of ocular surface squamous neoplasia which can manifest on the conjunctiva and cornea and have been shown to require longer and more aggressive chemotherapeutic treatment [19,42].

TREATMENT

The treatment of AKC is focused on managing the acute flares as well as the long-term disease process.

Goals are to decrease symptomatology as well as to prevent permanent, vision-threatening sequelae. Many of the treatment principals utilized for atopic dermatitis can be applied to AKC. Identification and avoidance of triggers has been suggested as the first step; however, this is often difficult due to large number and abundance of triggers [18]. Instillation of over the counter artificial tear lubrication drops can improve symptoms of mild conjunctivitis, protect the barrier function of conjunctiva, dilute allergens and decrease the itch response. Topical synthetic adrenergic agents, or ocular decongestants, improve conjunctival injection but have little effect on decrease in itching. They can lead to a down regulation of alpha-1 receptors which can cause a rebound hyperemia [43].

Topical corticosteroids are used to treat acute exacerbations in all allergic conjunctivitis subtypes. Topical corticosteroids decrease proinflammatory cytokines and adhesion molecules through interaction with cytoplasmic glucocorticoid receptor. The goal of therapy is the use corticosteroids to quickly improve symptoms and signs of disease and then switch to an agent with a more favorable side effect profile. That is because the long-term use of corticosteroids produces side effects of increases in intraocular pressure and cataract formation [44].

Once the acute exacerbation is controlled, topical antihistamines are used for symptom management in seasonal and perennial allergic conjunctivitis. These agents are usually not effective in AKC. Antihistamines target H1 receptors to prevent pruritis. Second-generation antihistamines are preferred as they are more specific and avoid side effects of sedation, by way of having high specificity for the H1 receptor (examples include levocabastine, azelastine, emedastine and bepotastine) [43]. Oral antihistamines are used in the treatment of systemic symptoms but can have a slower onset of action for the treatment of ocular manifestations and can exacerbate dry eye [45].

Topical mast cell stabilizers prevent mast cell degranulation via calcium influx and chloride efflux [46–48]. They have been shown to decrease itching in clinical trials versus placebo [37]. Common mast cell stabilizers include lodoxamide, nedocromil sodium, pemirolast. Combination mast cell stabilizers and antihistamines are most often used in symptom management, and in some trials, have shown to have a longer duration of symptom relief and better tolerability than single-acting antihistamines [37,49]. They have also been shown to improve comfort in contact lens wearers [50]. As above, these therapies are often used as first line agents in seasonal and perennial allergic conjunctivitis but are usually not effective in AKC. Common

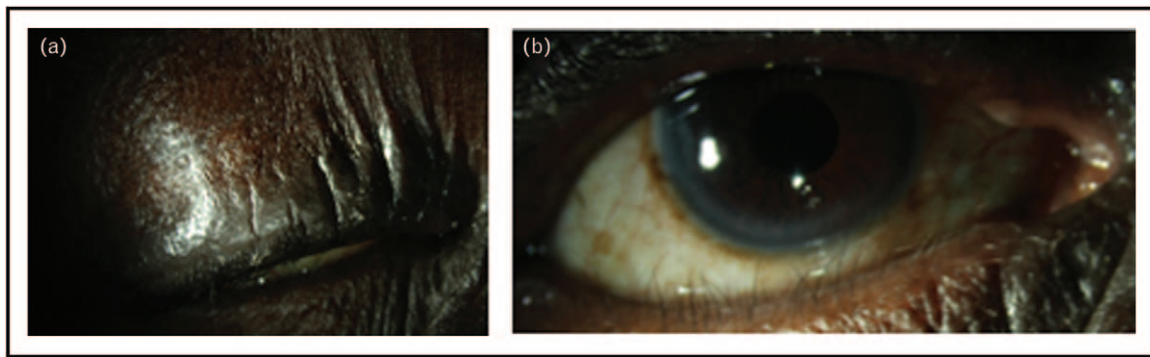


FIGURE 2. (a) Slit lamp photograph documenting improvement in lid hyperpigmentation and lichenification after topical steroid cream and oral tacrolimus use in atopic keratoconjunctivitis. (b) Slit lamp photograph documenting improvement in conjunctival hyperemia and papillary hypertrophy after oral tacrolimus in atopic keratoconjunctivitis.

combination topical drops include olopatadine and ketotifen. Less frequently used are the topical NSAIDs. However, these agents can also reduce symptoms of allergic conjunctivitis through a reduction of prostaglandin production [51].

Given the pathophysiology of AKC, chronic T-cell modulation is the favored approach for this allergic conjunctivitis subtype. Several agents modulate T-cell function including the calcineurin inhibitors, cyclosporine and FK506 (tacrolimus). These agents can be dosed topically [52], sublingually, subcutaneously and orally [53].

For moderate-to-severe atopic dermatitis, systemic cyclosporine A is the recommended first line treatment as a short-term option over systemic steroids. For ocular involvement, randomized control trials of topical 0.05% cyclosporine A have shown safety as well as improvement in signs and symptoms in allergic conjunctivitis as well as of AKC in mild and refractory cases [54,55]. In a similar manner, topical tacrolimus reduced signs and symptoms of AKC as a 0.1% solution or a 0.03% ointment. The concern with using these medications is the possibility of an increased risk of herpes simplex keratitis as well as eye irritation [56]. Systemic tacrolimus is reserved for cases that are refractory to local therapy [57]. The authors have found this as a safe and effective option in their patient population.

In the future, other agents that block T cells and/or other immune pathways may be beneficial in AKC. For example, dupilumab blocks IL-4/IL-13 signaling and has shown positive results in atopic dermatitis scoring systems in phase III clinical trials [58]. There is, however, a possible link to worsening conjunctival injection [59^{***}].

Clinical vignette

A 47-year-old male presented for evaluation of atopic conjunctivitis and dermatitis. He previously

had consultations with multiple subspecialists, including allergists, ophthalmologists and dermatologists, and had been trialed on a variety of treatments in the preceding 5 years including topical and oral steroids. On initial presentation, the patient complained of severe itching of the eyes and skin. The exam showed severe dermatitis of the face and body. The eyelids had notable hyperpigmentation and lichenification (Fig. 1a). The conjunctiva showed marked injection and the cornea had a diffusely irritated epithelial layer. The patient was placed on artificial tears and topical fluorometholone with minimal improvement. Given the severe and widespread disease, the patient was started on oral tacrolimus 5 mg daily. He had a dramatic response with marked improvement of both dermatitis and conjunctivitis within 1 month (Fig. 2a and b). He continued to improve and remained relapse free over the course of a 2 year follow-up.

CONCLUSION

Ocular involvement in atopic disease can have a variety of clinical manifestations, affecting the periocular skin, conjunctiva, and cornea. Its symptomatology, disease course and pathophysiology helps distinguish it from other allergic conjunctivitis processes. Progressive ocular disease can be potentially vision threatening. Prompt and effective treatment through a multidisciplinary approach, including ophthalmology, allergy and immunology and dermatology can permit stability of the disease.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Nelson HS. What is atopy? Sidestepping semantics. *Postgrad Med* 1984; 76:118–120; 123–129.
2. Thomsen SF. Epidemiology and natural history of atopic diseases. *Eur Clin Respir J* 2015; 2.
3. Hogan MJ. Atopic keratoconjunctivitis. *Am J Ophthalmol* 1953; 36:937–947.
4. Spergel JM. Immunology and treatment of atopic dermatitis. *Am J Clin Dermatol* 2008; 9:233–244.
5. Hu Y, Matsumoto Y, Dogru M, *et al*. The differences of tear function and ocular surface findings in patients with atopic keratoconjunctivitis and vernal keratoconjunctivitis. *Allergy* 2007; 62:917–925.
6. Avunduk AM, Avunduk MC, Dayanir V, Tekelioglu Y. Further studies on the immunopathology of atopic keratoconjunctivitis using flow cytometry. *Exp Eye Res* 1997; 65:803–808.
7. Hingorani M, Calder V, Jolly G, *et al*. Eosinophil surface antigen expression and cytokine production vary in different ocular allergic diseases. *J Allergy Clin Immunol* 1998; 102:821–830.
8. Metz DP, Hingorani M, Calder VL, *et al*. T-cell cytokines in chronic allergic eye disease. *J Allergy Clin Immunol* 1997; 100(6 Pt 1):817–824.
9. Gugliemetti S, Dart JK, Calder V. Atopic keratoconjunctivitis and atopic dermatitis. *Curr Opin Allergy Clin Immunol* 2010; 10:478–485.
10. Matsuda A, Ebihara N, Yokoi N, *et al*. Functional role of thymic stromal lymphopoietin in chronic allergic keratoconjunctivitis. *Invest Ophthalmol Vis Sci* 2010; 51:151–155.
11. Matsuda A, Okayama Y, Terai N, *et al*. The role of interleukin-33 in chronic allergic conjunctivitis. *Invest Ophthalmol Vis Sci* 2009; 50:4646–4652.
12. Matsuda A, Ebihara N, Yokoi N, *et al*. Basophils in the giant papillae of chronic allergic keratoconjunctivitis. *Br J Ophthalmol* 2010; 94:513–518.
13. Leung DY, Boguniewicz M, Howell MD, *et al*. New insights into atopic dermatitis. *J Clin Invest* 2004; 113:651–657.
14. Tuft SJ, Ramakrishnan M, Seal DV, *et al*. Role of *Staphylococcus aureus* in chronic allergic conjunctivitis. *Ophthalmology* 1992; 99:180–184.
15. Zhan H, Smith L, Calder V, *et al*. Clinical and immunological features of atopic keratoconjunctivitis. *Int Ophthalmol Clin* 2003; 43:59–71.
16. Tuft SJ, Kemeny DM, Dart JK, Buckley RJ. Clinical features of atopic keratoconjunctivitis. *Ophthalmology* 1991; 98:150–158.
17. Foster CS, Calonge M. Atopic keratoconjunctivitis. *Ophthalmology* 1990; 97:992–1000.
18. Bielory B, Bielory L. Atopic dermatitis and keratoconjunctivitis. *Immunol Allergy Clin North Am* 2010; 30:323–336.
19. Chen JJ, Applebaum DS, Sun GS, Pflugfelder SC. Atopic keratoconjunctivitis: a review. *J Am Acad Dermatol* 2014; 70:569–575.
20. Dogru M, Okada N, Asano-Kato N, *et al*. Alterations of the ocular surface epithelial mucins 1, 2, 4 and the tear functions in patients with atopic keratoconjunctivitis. *Clin Exp Allergy* 2006; 36:1556–1565.
21. Power WJ, Tugal-Tutkun I, Foster CS. Long-term follow-up of patients with atopic keratoconjunctivitis. *Ophthalmology* 1998; 105:637–642.
22. Shaker M, Salcone E. An update on ocular allergy. *Curr Opin Allergy Clin Immunol* 2016; 16:505–510.
- The review gives a complete overview of the allergic type conjunctivitis as well as a detailed review of the pathophysiology.
23. Ono SJ, Abelson MB. Allergic conjunctivitis: update on pathophysiology and prospects for future treatment. *J Allergy Clin Immunol* 2005; 115:118–122.
24. Bonini S. Allergic conjunctivitis: the forgotten disease. *Chem Immunol Allergy* 2006; 91:110–120.
25. Bonini S, Gramiccioni C, Bonini M, Bresciani M. Practical approach to diagnosis and treatment of ocular allergy: a 1-year systematic review. *Curr Opin Allergy Clin Immunol* 2007; 7:446–449.
26. Friedlaender MH. Conjunctivitis of allergic origin: clinical presentation and differential diagnosis. *Surv Ophthalmol* 1993; 38 Suppl:105–114.
27. Amemiya T, Matsuda H, Uehara M. Ocular findings in atopic dermatitis with special reference to the clinical features of atopic cataract. *Ophthalmologica* 1980; 180:129–132.
28. Shu DY, Ong K, Lovicu FJ. Histopathology of subcapsular cataract in a patient with atopic dermatitis. *Optom Vis Sci* 2017; 94:270–276.
29. Matsuda A, Ebihara N, Kumagai N, *et al*. Genetic polymorphisms in the promoter of the interferon gamma receptor 1 gene are associated with atopic cataracts. *Invest Ophthalmol Vis Sci* 2007; 48:583–589.
30. Sim DA, Chen RP, Hove M, Verma S. Acute irreversible cortical cataracts in prolonged topical corticosteroid overuse for chronic eczema. *Eye* 2009; 23:984.
31. Mondzelewski L, Hagan C, White A. An 18-year-old male with severe bilateral cataracts and atopic dermatitis – a case report and review of the literature. *Pediatr Dermatol* 2009; 26:583–586.
32. Bair B, Dodd J, Heidelberg K, Krach K. Cataracts in atopic dermatitis: a case presentation and review of the literature. *Arch Dermatol* 2011; 147: 585–588.
33. Harrison RJ, Klouda PT, Easty DL, *et al*. Association between keratoconus and atopy. *Br J Ophthalmol* 1989; 73:816–822.
34. Shajari M, Eberhardt E, Muller M, *et al*. Effects of atopic syndrome on keratoconus. *Cornea* 2016; 35:1416–1420.
35. Tomita M, Shimmura S, Tsubota K, Shimazaki J. Postkeratoplasty atopic sclerokeratitis in keratoconus patients. *Ophthalmology* 2008; 115:851–856.
36. Neira W, Krotila K, Holopainen JM. Atopic dermatitis is a risk factor for intracorneal ring segment extrusion. *Acta Ophthalmol* 2014; 92:e491–e492.
37. Bielory L. Allergic and immunologic disorders of the eye. Part II: Ocular allergy. *J Allergy Clin Immunol* 2000; 106:1019–1032.
38. Oshinskie L, Haine C. Atopic dermatitis and its ophthalmic complications. *J Am Optom Assoc* 1982; 53:889–894.
39. Easty D, Entwistle C, Funk A, Witcher J. Herpes simplex keratitis and keratoconus in the atopic patient. A clinical and immunological study. *Trans Ophthalmol Soc U K* 1975; 95:267–276.
40. Kothari N, Young RC, Read SP, *et al*. Retinal detachment associated with atopic dermatitis. *Ophthalmic Surg Lasers Imaging Retin* 2017; 48:513–517.
41. Hurlbut WB, Dornonkos AN. Cataract and retinal detachment associated with atopic dermatitis. *AMA Archiv Ophthalmol* 1954; 52:852–857.
42. Zhang L, Mercado C, Galor A, *et al*. Challenging treatment of ocular surface squamous neoplasia in patients with atopic disease. *Ocul Immunol Inflamm* 2017; 1–6. [Epub ahead of print]
43. Bielory L, Meltzer EO, Nichols KK, *et al*. An algorithm for the management of allergic conjunctivitis. *Allergy Asthma Proc* 2013; 34:408–420.
44. Camahan MC, Goldstein DA. Ocular complications of topical, peri-ocular, and systemic corticosteroids. *Curr Opin Ophthalmol* 2000; 11:478–483.
45. Ousler GW, Wilcox KA, Gupta G, Abelson MB. An evaluation of the ocular drying effects of 2 systemic antihistamines: loratadine and cetirizine hydrochloride. *Ann Allergy Asthma Immunol* 2004; 93:460–464.
46. Allansmith MR, Ross RN. Ocular allergy and mast cell stabilizers. *Surv Ophthalmol* 1986; 30:229–244.
47. Janssen LJ, Wattie J, Betti PA. Effects of cromolyn and nedocromil on ion currents in canine tracheal smooth muscle. *Eur Respir J* 1998; 12:50–56.
48. Alton EW, Norris AA. Chloride transport and the actions of nedocromil sodium and cromolyn sodium in asthma. *J Allergy Clin Immunol* 1996; 98(5 Pt 2):S102–S105; discussion S105–S106.
49. Abelson MB, Spitalny L. Combined analysis of two studies using the conjunctival allergen challenge model to evaluate olopatadine hydrochloride, a new ophthalmic antiallergic agent with dual activity. *Am J Ophthalmol* 1998; 125:797–804.
50. Nichols KK, Morris S, Gaddie IB, Evans D. Epinastine 0.05% ophthalmic solution in contact lens-wearing subjects with a history of allergic conjunctivitis. *Eye Contact Lens* 2009; 35:26–31.
51. Tinkelman DG, Rupp G, Kaufman H, *et al*. Double-masked, paired-comparison clinical study of ketorolac tromethamine 0.5% ophthalmic solution compared with placebo eyedrops in the treatment of seasonal allergic conjunctivitis. *Surv Ophthalmol* 1993; 38 Suppl:133–140.
52. Yin Z, Xu J, Luo D. Efficacy and tolerance of tacrolimus and pimecrolimus for atopic dermatitis: a meta-analysis. *J Biomed Res* 2011; 25:385–391.
53. Calderon MA, Penagos M, Sheikh A, *et al*. Sublingual immunotherapy for allergic conjunctivitis: Cochrane systematic review and meta-analysis. *Clin Exp Allergy* 2011; 41:1263–1272.
54. Akpek EK, Dart JK, Watson S, *et al*. A randomized trial of topical cyclosporin 0.05% in topical steroid-resistant atopic keratoconjunctivitis. *Ophthalmology* 2004; 111:476–482.
55. Daniell M, Constantinou M, Vu HT, Taylor HR. Randomised controlled trial of topical ciclosporin A in steroid dependent allergic conjunctivitis. *Br J Ophthalmol* 2006; 90:461–464.
56. Westland T, de Bruin-Weller MS, Van der Lelij A. Treatment of atopic keratoconjunctivitis in patients with atopic dermatitis: is ocular application of tacrolimus an option? *J Eur Acad Dermatol Venereol* 2013; 27: 1187–1189.
57. Stumpf T, Luqmani N, Sumich P, *et al*. Systemic tacrolimus in the treatment of severe atopic keratoconjunctivitis. *Cornea* 2006; 25:1147–1149.
58. Seegraber M, Srouf J, Walter A, *et al*. Dupilumab for treatment of atopic dermatitis. *Exp Rev Clin Pharmacol* 2018; 11:467–474.
59. Ou Z, Chen C, Chen A, *et al*. Adverse events of Dupilumab in adults with ■ moderate-to-severe atopic dermatitis: a meta-analysis. *Int Immunopharmacol* 2018; 54:303–310.

This is an important meta-analysis that reviews the adverse events of new therapeutic agent in atopic dermatitis. This treatment could be a possible tool for the treatment of atopic keratoconjunctivitis.